INTERNATIONAL STANDARD

ISO 18562-1

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Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 1: Evaluation and testing within a risk management process

Évaluation de la biocompatibilité des voies de gaz respiratoires dans les applications de soins de santé —

Partie 1: Évaluation et essais au sein d'un processus de gestion du risque

Reference number
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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of ISO standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

The committee responsible for this document is ISO/TC 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 3, *Lung ventilators and related equipment*.

A list of all parts in the ISO 18562 series can be found on the ISO website.

Introduction

This document represents the application of the best-known science, in order to improve PATIENT safety, by addressing the RISK of potentially hazardous substances being conveyed to the PATIENT by the gas stream.

This document is intended to cover the biological evaluation of GAS PATHWAYS of MEDICAL DEVICES within a RISK MANAGEMENT PROCESS, as part of the overall MEDICAL DEVICE evaluation and development. This approach combines the review and evaluation of existing data from all sources with, where necessary, the selection and application of additional tests.

In general, the ISO 10993 series is intended to cover the biological evaluation of MEDICAL DEVICES. However, the ISO 10993 series does not sufficiently address the biological evaluation of the GAS PATHWAYS of MEDICAL DEVICES.

Before this document was developed, some AUTHORITIES HAVING JURISDICTION interpreted the ISO 10993-1:2009, Table A.1 to mean that materials in the GAS PATHWAY form “indirect contact” with the PATIENT, and should be subjected to tests equivalent to those required for tissue contact parts of MEDICAL DEVICES. This interpretation can lead to tests with questionable benefit and also to possible HAZARDS not being detected.

ISO 10993-1:2009 states that it is not intended to provide a rigid set of test methods as this might result in an unnecessary constraint on the development and use of novel MEDICAL DEVICES. ISO 10993-1:2009 also states where a particular application warrants it, experts in the product or in the area of application concerned can choose to establish specific tests and criteria, described in a product-specific vertical standard. This new series of standards is intended to address the specific needs for the evaluation of GAS PATHWAYS that are not adequately covered by ISO 10993-1:2009.

This document provides a guide to the development of a biological evaluation plan that minimizes the number and exposure of test animals by giving preference to chemical constituent testing and *in vitro* models.

The initial version of this series of standards was intended to cover only the most commonly found potentially harmful substances. It was felt that it was best to get a functioning document published that would test for the bulk of the currently known substances of interest. With the use of the TTC (THRESHOLD OF TOXICOLOGICAL CONCERN) approach, this document has the potential to be used to assess the safety of essentially any compound released from the GAS PATHWAYS of respiratory MEDICAL DEVICES, with very few exceptions (e.g. PCBs, dioxins), and not just the most commonly found potentially harmful substances. Later amendments and additional parts are planned to explicitly cover less common substances.

In this document, the following print types are used:

— requirements and definitions: roman type;

— *test specifications: italic type*;

— informative material appearing outside of tables, such as notes, examples and references: in smaller type. Normative text of tables is also in a smaller type;

— terms defined in Clause 3 of this DOCUMENT or as noted: small capitals.

In this document, the conjunctive “or” is used as an “inclusive or” so a statement is true if any combination of the conditions is true.

The verbal forms used in this document conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this document, the auxiliary verb:

— “shall” means that compliance with a requirement or a test is mandatory for compliance with this document;

— "should" means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this document;

— "may" is used to describe a permissible way to achieve compliance with a requirement or test.

An asterisk (*) as the first character of a title or at the beginning of a paragraph or table title indicates that there is guidance or rationale related to that item in Annex A.

The attention of Member Bodies is drawn to the fact that equipment manufacturers and testing organizations may need a transitional period following publication of a new, amended or revised ISO or IEC publication in which to make products in accordance with the new requirements and to equip themselves for conducting new or revised tests. It is the recommendation of the committee that the content of this publication be adopted for implementation nationally not earlier than 3 years from the date of publication for equipment newly designed and not earlier than 5 years from the date of publication for equipment already in production.

Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 1: Evaluation and testing within a risk management process

1 Scope

This document specifies:

— the general principles governing the biological evaluation within a RISK MANAGEMENT PROCESS of the GAS PATHWAYS of a MEDICAL DEVICE, its parts or ACCESSORIES, which are intended to provide respiratory care or supply substances via the respiratory tract to a PATIENT in all environments;

— the general categorization of GAS PATHWAYS based on the nature and duration of their contact with the gas stream;

— the evaluation of existing relevant data from all sources;

— the identification of gaps in the available data set on the basis of a RISK ANALYSIS;

— the identification of additional data sets necessary to analyse the biological safety of the GAS PATHWAY;

— the assessment of the biological safety of the GAS PATHWAY.

This document covers general principles regarding BIOCOMPATIBILITY assessment of MEDICAL DEVICE materials, which make up the GAS PATHWAY, but does not cover biological HAZARDS arising from any mechanical failure, unless the failure introduces a toxicity RISK (e.g. by generating PARTICULATES). The other parts of ISO 18562 cover specific tests that address potentially hazardous substances that are added to the respirable gas stream and establish acceptance criteria for these substances.

This document addresses potential contamination of the gas stream arising from the GAS PATHWAYS within the MEDICAL DEVICE, which might then be conducted to the PATIENT.

This document applies over the EXPECTED SERVICE LIFE of the MEDICAL DEVICE in NORMAL USE and takes into account the effects of any intended processing or reprocessing.

This document does not address biological evaluation of the surfaces of MEDICAL DEVICES that are in direct contact with the PATIENT. The requirements for direct contact surfaces are found in the ISO 10993 series.

MEDICAL DEVICES, parts or ACCESSORIES containing GAS PATHWAYS that are addressed by this document include, but are not limited to, ventilators, anaesthesia workstations (including gas mixers), breathing systems, oxygen conserving equipment, oxygen concentrators, nebulizers, low-pressure hose assemblies, humidifiers, heat and moisture exchangers, respiratory gas monitors, respiration monitors, masks, mouth pieces, resuscitators, breathing tubes, breathing system filters and Y-pieces as well as any breathing ACCESSORIES intended to be used with such MEDICAL DEVICES. The enclosed chamber of an incubator, including the mattress, and the inner surface of an oxygen hood are considered to be GAS PATHWAYS and are also addressed by this document.

This document does not address contamination already present in the gas supplied from the gas sources while MEDICAL DEVICES are in NORMAL USE.

EXAMPLE Contamination arriving at the MEDICAL DEVICE from gas sources such as MEDICAL GAS PIPELINE SYSTEMS (including the non-return valves in the pipeline outlets), outlets of pressure regulators connected or integral to a medical gas cylinder, or room air taken into the MEDICAL DEVICE is not addressed by ISO 18562 (all parts).

Future parts might be added to address other relevant aspects of biological testing including additional contamination that might arise from the GAS PATHWAY because of the presence of drugs and anaesthetic agents added to the gas stream.

NOTE 1 Some AUTHORITIES HAVING JURISDICTION require evaluation of these RISKS as part of a biological evaluation.

NOTE 2 This document has been prepared to address the relevant essential principles of safety and performance as indicated in Annex B.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 7396-1:2016, *Medical gas pipeline systems — Part 1: Pipeline systems for compressed medical gases and vacuum*

ISO 10993-1:2009, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-17:2002, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

ISO 18562-2, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 2: Tests for emissions of particulate matter*

ISO 18562-3, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 3: Tests for emissions of volatile organic compounds (VOCs)*

ISO 18562-4, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 4: Tests for leachables in condensate*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 7396-1, ISO 14971 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at http://www.iso.org/obp

NOTE For convenience, an alphabetized index of all defined terms and their sources used in this document is given in Annex C.

3.1
ACCESSORY
additional part for use with a MEDICAL DEVICE in order to:

— achieve the INTENDED USE,

— adapt it to some special use,

— facilitate its use,

— enhance its performance, or

— enable its function to be integrated with those of other MEDICAL DEVICES

[SOURCE: IEC 60601-1:2005, 3.3, modified — substituted "MEDICAL DEVICE" for "equipment"]

3.2
BIOCOMPATIBILITY
ability to be in contact with a living system without producing an unacceptable adverse effect

Note 1 to entry: MEDICAL DEVICES may produce some level of adverse effect, but that level may be determined to be acceptable when considering the benefits provided by the MEDICAL DEVICE.

3.3
EXPECTED SERVICE LIFE
maximum period of useful life as defined by the MANUFACTURER

[SOURCE: IEC 60601-1:2005+AMD1:2012, 3.28]

3.4
FORMULATION
base polymer or alloy, including additives, colours, etc. used to establish a property or the stability of the material

Note 1 to entry: This does not include processing aids, mould release agents, residual contaminants, or other manufacturing aids that are not intended to be a part of the material.

Note 2 to entry: The term "chemical composition" is commonly used as a synonym for FORMULATION.

[SOURCE: US FDA 510(k) Memorandum #K97-1]

3.5
GAS PATHWAY
interior surfaces, over which gases or liquids that can be inspired, in a MEDICAL DEVICE bounded by the ports through which gases or liquids enter and leave the MEDICAL DEVICE including the PATIENT interface or the interior surfaces of enclosures that are in contact with gases or liquids that can be inspired

Note 1 to entry: PATIENT contact surfaces such as the outer surfaces of a tracheal tube or the cushion of a mask are evaluated according to the ISO 10993 series.

EXAMPLE 1 The ventilator breathing system, inlet filter, gas mixer, blower and internal piping.

EXAMPLE 2 Enclosed chamber of an incubator including the mattress or the inner surface of an oxygen hood.

EXAMPLE 3 The inner surfaces of breathing tubes, tracheal tubes or masks and mouthpieces.

3.6
LEACHABLE SUBSTANCE
chemical removed from a MEDICAL DEVICE by the action of water, other liquids or other gases (e.g. anaesthetic agents or inhalational drugs) related to the use of the MEDICAL DEVICE

EXAMPLE Additives, sterilant residues, PROCESS residues, degradation products, solvents, plasticizers, lubricants, catalysts, stabilizers, anti-oxidants, colouring agents, fillers and monomers, among others.

[SOURCE: ISO 10993-17:2002, 3.10, modified — added "or other gases (e.g. anaesthetic agents or inhalational drugs)"]

3.7
MEDICAL DEVICE
instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the MANUFACTURER to be used, alone or in combination, for human beings for one or more of the following specific purpose(s) of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy or of a physiological PROCESS;

— supporting or sustaining life;

— control of conception;

— disinfection of MEDICAL DEVICES;

— providing information by means of *in vitro* examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means

Note 1 to entry: Products which may be considered to be MEDICAL DEVICES in some jurisdictions but not in others include:

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for *in vitro* fertilization or assisted reproduction technologies.

[SOURCE: ISO 13485:2016, 3.11]

3.8
NORMAL CONDITION
condition in which all means provided for protection against HAZARDS are intact

[SOURCE: IEC 60601-1:2005, 3.70]

3.9
NORMAL USE
operation, including routine inspection and adjustments by any user, and stand-by, according to the instructions for use

Note 1 to entry: NORMAL USE should not be confused with INTENDED USE. While both include the concept of use as intended by the MANUFACTURER, INTENDED USE focuses on the medical purpose while NORMAL USE incorporates not only the medical purpose but maintenance, service, transport, etc. as well.

[SOURCE: IEC 60601-1:2005+AMD1:2012, 3.97, modified — replaced “OPERATOR” with “user”]

3.10
PARTICULATE MATTER
PM
PARTICULATES
solid particles suspended in a gas

3.11
PATIENT
living human undergoing a medical, surgical, or dental procedure

[SOURCE: IEC 60601-1:2005+AMD1:2012, 3.76, modified — removed reference to animal]

3.12
THRESHOLD OF TOXICOLOGICAL CONCERN
TTC
level of exposure for all chemicals, known or unknown, below which it is considered there is no appreciable RISK to human health

Note 1 to entry: A TTC is used as an acceptable value for a TE for an unknown or insufficiently characterized compound.

3.13
TOLERABLE EXPOSURE
TE
total amount of a substance (in units of μg/d) that a PATIENT can be exposed to per 24 h period that is considered to be without appreciable harm to health

Note 1 to entry: TE is also referred to as "allowed dose to patient". This amount is specific to a particular PATIENT or PATIENT group of a given body weight.

Note 2 to entry: TE is calculated by multiplying TOLERABLE INTAKE by the body mass.

3.14
TOLERABLE INTAKE
TI
TOLERABLE INTAKE LEVEL
TIL
total amount of a substance per kilogram of body weight (in units of μg/kg body weight/d) that a PATIENT can be exposed to per 24 h period that is considered to be without appreciable harm to health

Note 1 to entry: This amount is applicable for all PATIENT groups.

3.15
TYPE TEST
test on a representative sample of the MEDICAL DEVICE with the objective of determining if the MEDICAL DEVICE, as designed and manufactured, can meet the requirements of this document

Note 1 to entry: If the final MEDICAL DEVICE is not used for the assessments, all differences between the "representative sample" and the final MEDICAL DEVICE need to be described and a justification provided for why the differences do not affect the outcome of the testing.

[SOURCE: IEC 60601-1:2005, 3.135, modified — substituted "MEDICAL DEVICE" for "me equipment" and added Note 1]

3.16
VOLATILE ORGANIC COMPOUND
VOC
organic compound whose boiling point is in the range of 50 °C to 260 °C

Note 1 to entry: There are many varied definitions of VOC. For the purposes of this document, a VOC is a compound that has a boiling point in the range of 50 °C to 260 °C, at a standard atmospheric pressure of 101,3 kPa.

Note 2 to entry: Boiling points of some compounds are difficult or impossible to determine because they decompose before they boil at atmospheric pressure.

Note 3 to entry: Compounds still exert a vapour pressure, and so could enter the breathing gas, at temperatures lower than their boiling point.

Note 4 to entry: VOC does not include VERY VOLATILE ORGANIC COMPOUNDS (VVOCS) nor semi-volatile organic compounds (SVOCs). Additional parts of this document might be developed to address these substances in the future. Some AUTHORITIES HAVING JURISDICTION require evaluation of these RISKS as part of a biological evaluation.

3.17
VERY VOLATILE ORGANIC COMPOUND
VVOC
organic compound whose boiling point is in the range of 0 °C to 50 °C

Note 1 to entry: Boiling points of some compounds are difficult or impossible to determine because they decompose before they boil at atmospheric pressure.

4 General principles applying to BIOCOMPATIBILITY evaluation of MEDICAL DEVICES

4.1 General

The BIOCOMPATIBILITY evaluation of any material or MEDICAL DEVICE, part or ACCESSORY intended for use with PATIENTS shall form part of a structured BIOCOMPATIBILITY evaluation programme within a RISK MANAGEMENT PROCESS. The BIOCOMPATIBILITY evaluation shall be planned, carried out and documented by knowledgeable and experienced professionals. Figure 1 illustrates this PROCESS.

The evaluation programme shall include documented, informed decisions that assess the advantages/disadvantages and relevance of:

— the physical and chemical characteristics of the various candidate materials over the EXPECTED SERVICE LIFE of the MEDICAL DEVICE;

NOTE Where this information is already documented within the RISK MANAGEMENT FILE for the MEDICAL DEVICE, it can be included by reference.

— any history of human exposure data;

— any existing toxicology and other BIOCOMPATIBILITY safety data on product and component materials, breakdown products and metabolites.

All MEDICAL DEVICES should be evaluated for BIOCOMPATIBILITY, but evaluation does not necessarily imply testing everything. Depending on the final FORMULATION, manufacturing or application, an evaluation may result in the conclusion that no testing or no additional testing is needed.

EXAMPLE The MEDICAL DEVICE has a demonstrable similarity in a specified function and physical form, has identical FORMULATION, contains no additional chemicals, uses the same manufacturing PROCESSES, so that it is equivalent to a MEDICAL DEVICE, part or ACCESSORY that has already been evaluated.

Check compliance by inspection of the RISK MANAGEMENT plan and RISK MANAGEMENT FILE.
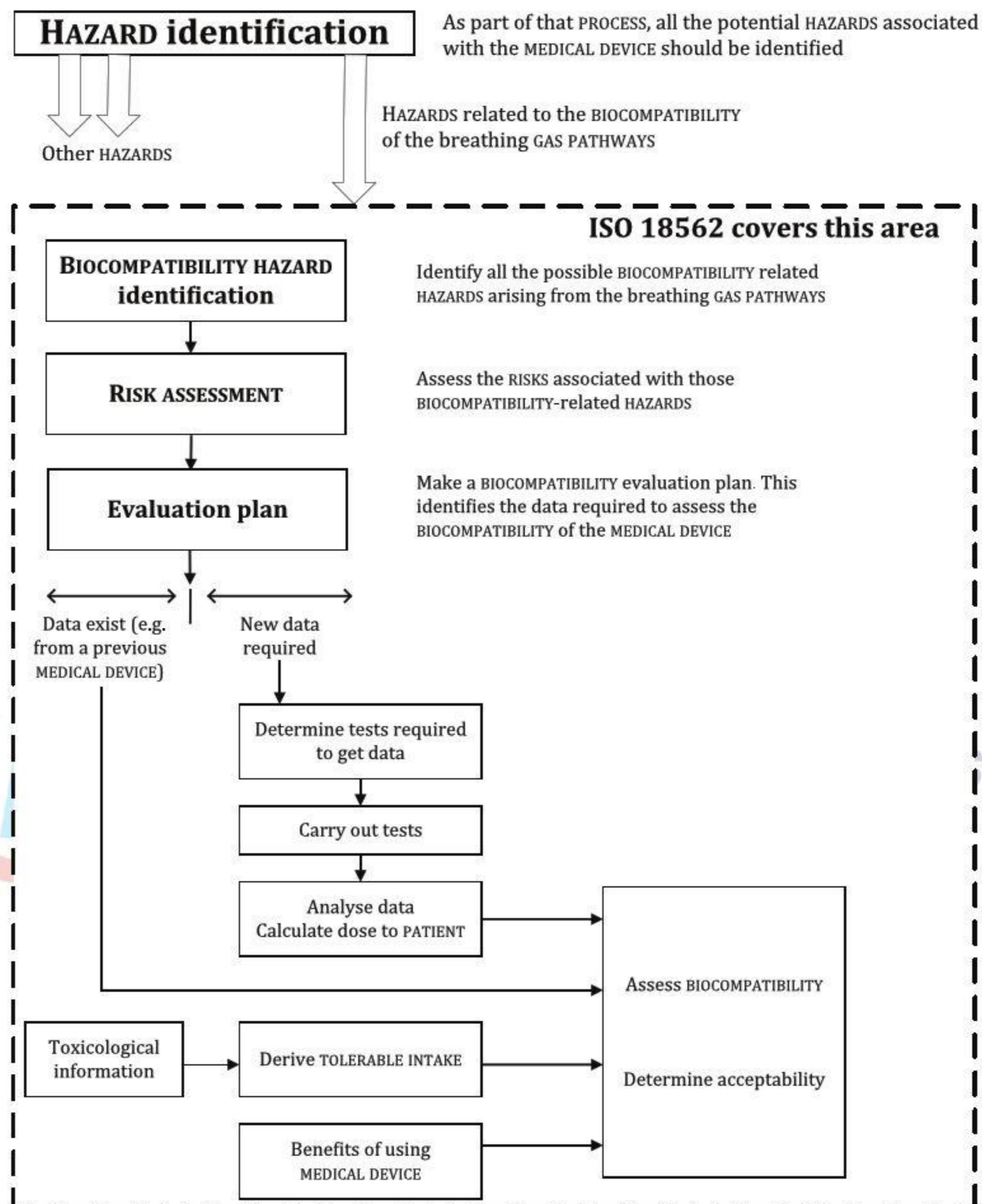
Figure 1 — RISK MANAGEMENT PROCESS for biological evaluation of GAS PATHWAYS

4.2 TYPE TESTS

The tests described in this document are TYPE TESTS. TYPE TESTS are performed on the final MEDICAL DEVICE, a component of the MEDICAL DEVICE or a representative sample of the MEDICAL DEVICE, part or ACCESSORY being evaluated. If representative samples are used (i.e. manufactured and processed by equivalent methods), consideration should be given to whether or not the differences between the representative sample and the final MEDICAL DEVICE or component could affect the results of the test. Testing of representative samples (manufactured and processed by equivalent methods) instead of the final MEDICAL DEVICE should be supported by a description of any differences between the

representative sample and the final MEDICAL DEVICE, and a detailed rationale for why each difference is not expected to impact the BIOCOMPATIBILITY of the final MEDICAL DEVICE.

NOTE Some AUTHORITIES HAVING JURISDICTION evaluate these differences and rationales.

4.3 BIOCOMPATIBILITY HAZARD identification

Identify all the possible BIOCOMPATIBILITY-related HAZARDS that might reach the PATIENT via the GAS PATHWAYS during the use of the MEDICAL DEVICE.

All known possible BIOCOMPATIBILITY-related HAZARDS shall be taken into account for every material and final MEDICAL DEVICE, part or ACCESSORY. This does not imply that testing for all possible HAZARDS is necessary or practical. ISO 10993-1:2009, Clause 5 and Clause 6 have additional requirements for additional types and durations of PATIENT exposure.

EXAMPLE For a MEDICAL DEVICE (such as a mask) that has direct PATIENT contact in addition to GAS PATHWAY contact, assessment for compliance to both ISO 18562-1 and ISO 10993-1 can be required.

In the selection of materials to be used in GAS PATHWAY manufacture, the first consideration should be fitness for purpose with regard to characteristics and properties of the material, which includes physical, mechanical, chemical and toxicological properties.

Materials used to manufacture the components in the GAS PATHWAYS should be suitable for the INTENDED USE, and use materials with demonstrable history of safe use in the intended or comparable application wherever possible.

The following shall be taken into account for their relevance to the overall biological evaluation of the GAS PATHWAY:

— the material(s) of manufacture;

— intended additives, PROCESS contaminants and residues;

— substances released in NORMAL USE;

— degradation products from NORMAL USE that might pass into the PATIENT via the GAS PATHWAYS;

NOTE 1 ISO 10993-9[1] contains requirements for general principles and ISO 10993-13[2], ISO 10993-14[3] and ISO 10993-15[4] contain requirements for degradation products from polymers, ceramics and metals, respectively. If testing for degradation using dry heat only, then ISO 10993-13, ISO 10993-14 and ISO 10993-15 need not apply.

NOTE 2 NORMAL USE can include use with heated and humidified breathing gas. Tests are done on the "worst case" configuration. This can mean testing with and without heat and humidification to establish the worst case.

— other components and their interactions in the final MEDICAL DEVICE, part or ACCESSORY;

— the performance and characteristics of the final MEDICAL DEVICE, part or ACCESSORY;

— physical characteristics of the final MEDICAL DEVICE, part or ACCESSORY including, but not limited to, porosity, particle size and shape;

— the effects of any hygienic processing steps required before use or re-use, if applicable.

Check compliance by inspection of the RISK MANAGEMENT plan and RISK MANAGEMENT FILE.

4.4 Extent of RISK ASSESSMENT

An analysis shall be made of the HAZARDS identified in 4.3, and the RISK that the HAZARD poses to the PATIENT determined. The results shall be documented.

NOTE 1 ISO 10993-1:2009, Figure 1 is a graphical representation of the RISK ASSESSMENT PROCESS.

The rigour necessary in the biological evaluation is principally determined by the duration and frequency of the exposure and the HAZARDS identified for the MEDICAL DEVICE. The information needed to support a biological evaluation, including any test data, shall take into account the physical and chemical characteristics of the materials, the electromechanical nature of the MEDICAL DEVICE, as well as the frequency, duration and conditions of exposure of the PATIENT to the gas from the GAS PATHWAY. This enables the categorization of uses to facilitate the selection of appropriate tests, if required.

NOTE 2 ISO 10993-1:2009, Clause 5 contains additional requirements.

4.5 BIOCOMPATIBILITY evaluation plan

Having identified the possible BIOCOMPATIBILITY HAZARDS and determined the RISKS that they might pose to the PATIENT, a BIOCOMPATIBILITY evaluation plan shall be created.

This plan shall detail what is currently known about the material FORMULATION, additives and PROCESS aids used in the manufacture of the GAS PATHWAYS of the MEDICAL DEVICE, and therefore identify gaps in knowledge that shall be filled by further work.

If a potential HAZARD has been identified, but the RISK it poses to the PATIENT can be shown to be negligible (for example, the dose the PATIENT receives is less than the TOLERABLE EXPOSURE), then no further work on the HAZARD is required. The decision shall be documented.

If a potential HAZARD has been identified, but the RISK it poses to the PATIENT is not negligible, or the RISK is unknown, then further work to characterize or mitigate the HAZARD is required. This step may involve referring to previous similar MEDICAL DEVICES and manufacturing methods, accessing reliable information in the public domain, or performing tests to gather the data.

All MEDICAL DEVICES should be evaluated for BIOCOMPATIBILITY, but evaluation does not automatically imply testing. Depending on the final FORMULATION, manufacturing and application, an evaluation may result in the conclusion that no testing or no additional testing is needed.

EXAMPLE The MEDICAL DEVICE has a demonstrable similarity in a specified function and physical form, has identical FORMULATION, contains no additional chemicals, uses the same manufacturing PROCESSES, so that it is equivalent to a MEDICAL DEVICE, part or ACCESSORY that has already been evaluated.

To reduce animal testing for GAS PATHWAYS that can contact liquids, identification of material chemical constituents and consideration of chemical characterization shall be undertaken, and only if results show the presence of substances, which do not have sufficient toxicological data to allow RISK ASSESSMENT, should any biological testing be considered.

NOTE 1 Some local effects including cytotoxicity, irritation, and sensitization might not be adequately assessed using a chemical characterization/RISK ASSESSMENT approach. As a result, it can be necessary to conduct biological testing to assess these end points. Systemic effects including acute, subacute, subchronic and chronic toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity can often be assessed using a chemical characterization/RISK ASSESSMENT approach.

An evaluation of PARTICULATE MATTER shall be included in the BIOCOMPATIBILITY evaluation.

Test results cannot guarantee freedom from potential biological HAZARDS. Thus, biological investigations shall be followed by careful observations for unexpected adverse reactions or events in humans during use of the final MEDICAL DEVICE, part or ACCESSORY.

NOTE 2 The range of possible biological HAZARDS is wide and can include short-term effects, as well as long-term or specific toxic effects.

The biological evaluation of a GAS PATHWAY shall take into account the nature and mobility of the chemical constituents in the materials used to manufacture the MEDICAL DEVICE, part or ACCESSORY and

other information, other non-clinical tests, clinical studies, and post-market experience for an overall assessment.

NOTE 3 This series does not currently address BIOCOMPATIBILITY HAZARDS associated with the following substances being added to the respirable gas stream. Nonetheless, when applicable, some AUTHORITIES HAVING JURISDICTION require the MANUFACTURER to evaluate the following:

— semi-volatile organic compounds and VVOCS;
— ozone, for GAS PATHWAYS in contact with active electromechanical or electrostatic parts in NORMAL CONDITION;
— CO and CO_2, for GAS PATHWAYS where inorganic gases are generated or concentrated;
— LEACHABLES, for GAS PATHWAYS in contact with anaesthetic agents where the gas can be inspired in NORMAL CONDITION;
— LEACHABLES, for GAS PATHWAYS in contact with substances intended to be delivered via the respiratory tract (e.g. inhalational drugs).

4.6 Selection of tests

The results of the BIOCOMPATIBILITY evaluation plan might indicate that further information is required. If this information is not available from other sources, then tests to complete the biological evaluation may be necessary.

The selection of tests shall be based on the conditions of expected worst-case clinical use (which could include repeated use). All tests shall be conducted according to recognized current/valid best laboratory/quality practices and the data shall be evaluated by competent, informed professionals.

NOTE Such test laboratories are operated under a recognized quality system, for example, ISO/IEC 17025[7].

Tests shall be carried out under clinically relevant environmental conditions, using clinically relevant flow rates and total flow volumes, and for clinically relevant time durations. For example, an emergency resuscitation device, which is used for a maximum of 20 min, should not be tested over a period of 24 h.

In vitro test methods, which are appropriately validated, reasonably and practically available, reliable and reproducible, shall be considered for use in preference to *in vivo* tests. Whenever possible, *in vitro* screening shall be carried out before *in vivo* tests are commenced. Test data, complete to the extent that an independent analysis could be made, shall be retained.

Where further tests may be required, the PROCESS depicted in Figure 2 shall be followed to identify the type of testing needed.

4.7 Subsequent evaluation

The materials or final MEDICAL DEVICE, part or ACCESSORY shall be re-evaluated if any of the following occurs:

— any change in the FORMULATION of the materials used in the manufacture, processing or primary packaging of the MEDICAL DEVICE, part or ACCESSORY;
— change in processing or reprocessing methods, including sterilization;
— any change in the MANUFACTURER'S instructions for use concerning storage (e.g. changes in shelf life or transport);
— any change in the INTENDED USE of the MEDICAL DEVICE, part or ACCESSORY;
— any other changes identified by RISK MANAGEMENT.

5 Contamination of breathing gas from GAS PATHWAYS

5.1 * Duration of use

The tests that a MEDICAL DEVICE, part or ACCESSORY shall be subjected to depend on the nature of the components in the GAS PATHWAY, its location in the GAS PATHWAY, and its duration of use on a PATIENT.

The tests and specified limits for a MEDICAL DEVICE may depend on its intended duration of use for a single PATIENT. This document addresses three different durations of use:

— limited exposure — MEDICAL DEVICE, part or ACCESSORY whose cumulative single, multiple or repeated use is less than or equal to 24 h;

— prolonged exposure — MEDICAL DEVICE, part or ACCESSORY whose cumulative single, multiple or repeated long-term use is likely to exceed 24 h but be less than 30 d;

NOTE 1 When determining if and what testing is needed for MEDICAL DEVICES that are in contact with the breathing gas, there are no differences in the biological effects for consideration between MEDICAL DEVICES with prolonged and permanent exposure.

— permanent contact — MEDICAL DEVICE, part or ACCESSORY whose cumulative single, multiple or repeated long-term use is likely to be equal to or exceed 30 d.

NOTE 2 The "duration" is duration of PATIENT exposure to the original plus subsequent replacement MEDICAL DEVICES, not duration of use of an individual MEDICAL DEVICE. There can be components replaced every few days so multiple sequential exposures to new replacement MEDICAL DEVICES need to be considered.
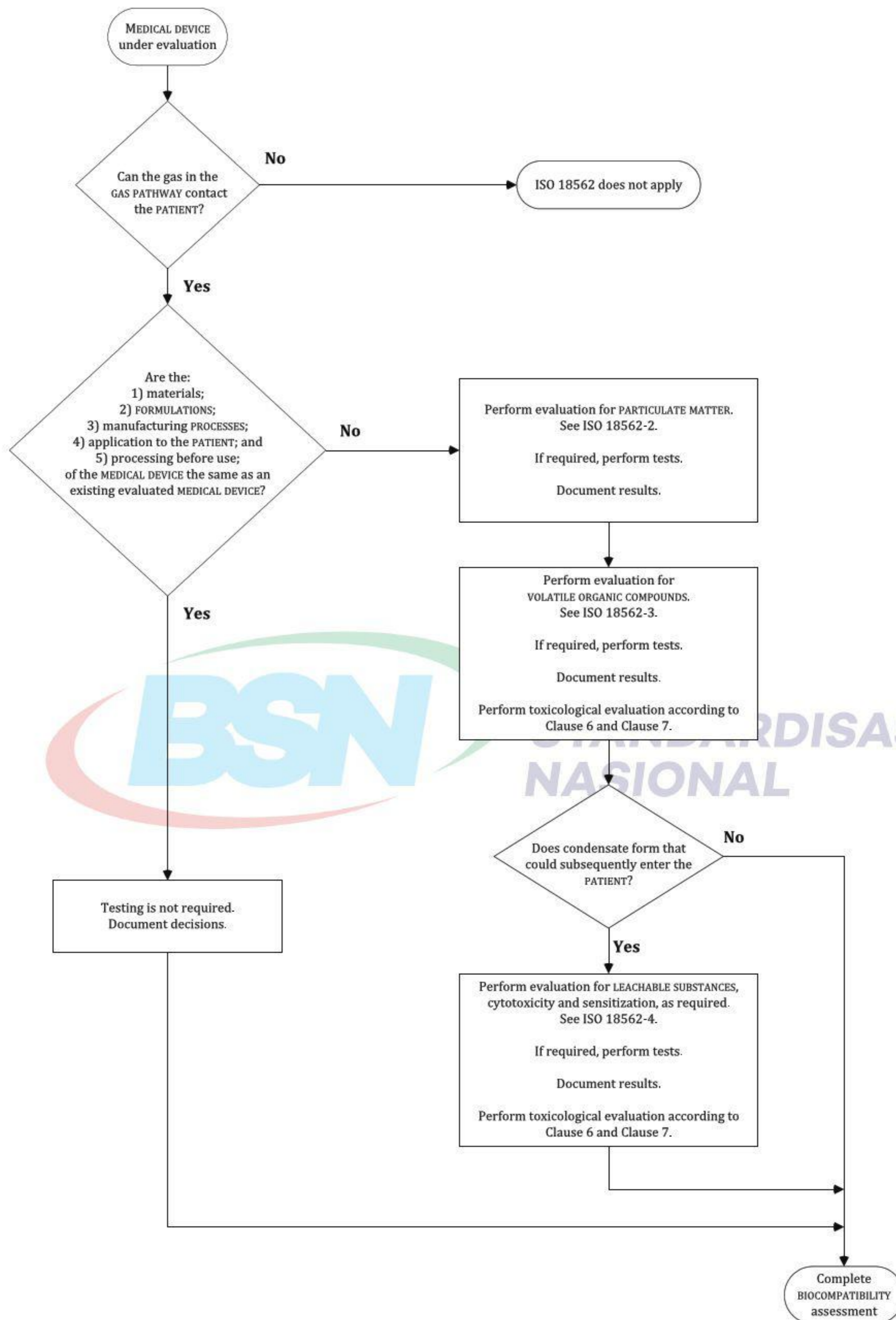
Figure 2 — Flowchart of PROCESS to determine what tests are to be considered

5.2 PARTICULATE MATTER (PM) emissions

All GAS PATHWAYS from which the PATIENT inspires gas shall be evaluated for PM emissions according to ISO 18562-2.

5.3 VOLATILE ORGANIC COMPOUND (VOC) emissions

All GAS PATHWAYS from which the PATIENT inspires gas shall be evaluated for VOC emissions according to ISO 18562-3.

NOTE Some AUTHORITIES HAVING JURISDICTION require evaluation of SVOCS and VVOCS.

5.4 LEACHABLE SUBSTANCES in condensate

If condensation can occur in the MEDICAL DEVICE and this condensate can reach the PATIENT, evaluation shall be performed for the presence of harmful LEACHABLE SUBSTANCES according to ISO 18562-4. Only sections of the GAS PATHWAY from which the PATIENT can be exposed to condensate need be tested. If the MEDICAL DEVICE under evaluation has already been evaluated as tissue contacting according to ISO 10993-1, then LEACHABLE SUBSTANCES tests need not be performed in addition.

6 Adjustment for different PATIENT groups

6.1 General considerations

The following guidance is offered to allow adjustment of permissible doses for different PATIENT groups. A more comprehensive coverage of this topic can be found in ISO 10993-17. The information offered here is simplified but remains sufficient for the purposes of this document. These adjustments may be used in calculating the permissible dose to which a PATIENT may be exposed for the tests of ISO 18562-3 (VOC) and ISO 18562-4 (condensate).

6.2 Adjustment for body weight

The small body weight of a neonate or paediatric PATIENT cannot tolerate the same dose of a toxic substance as an adult. A calculation is needed to compensate for the smaller body weight of these smaller PATIENTS.

TOLERABLE INTAKE values, in units of µg/kg body weight/d, are applicable for all PATIENT populations.

TOLERABLE EXPOSURE, in units of µg/d, is calculated when the TOLERABLE INTAKE is multiplied by body weight of that PATIENT or PATIENT group (see ISO 10993-17).

The default body weight values used to calculate TOLERABLE EXPOSURE in this document are the following (see ISO 10993-17:2002, Annex A):

— neonate 0,5 kg;

— infant 3,5 kg;

— paediatric 10 kg;

— adult 70 kg.

EXAMPLE If the TOLERABLE EXPOSURE (in µg/d) for a substance is known for an adult, then the TOLERABLE EXPOSURE for an infant PATIENT is 1/20th of the adult TOLERABLE EXPOSURE (because 3,5 kg/70 kg = 1/20).

Other body weight values, as appropriate, may be used to calculate TOLERABLE EXPOSURE.

6.3 * Deriving a permitted concentration from a TOLERABLE EXPOSURE

The fundamental consideration is "what is the dose to the PATIENT of this substance?" Limits for toxicological purposes are most often quoted as an absolute amount in µg/d (TOLERABLE EXPOSURE). Limits for environmental purposes, and the quantity that is measured by test laboratories, are usually quoted as concentrations, in µg/m^3. To work out the permitted concentration of that substance (in µg/m^3) in the breathing air, the total volume of air inhaled in a day is required.

The default breathing volumes used to calculate the dose to the PATIENT in any 24 h period are:

— neonate 0,21 m^3/d;

— infant 2,0 m^3/d;

— paediatric 5,0 m^3/d;

— adult 20 m^3/d.

The dose to the PATIENT depends on the concentration of the substance (in µg/m^3) multiplied by the volume (in m^3) inhaled by the PATIENT. A neonate PATIENT breathes a smaller total daily volume than an adult PATIENT. The following is relevant for continuous use (more than 24 h) MEDICAL DEVICES.

The inverse calculation — given a maximum permitted daily dose (a TOLERABLE EXPOSURE), what is the maximum permitted concentration of that substance in the breathing air? — is performed by taking the TOLERABLE EXPOSURE (in µg/d) and dividing by the number of cubic metres breathed in a day.

EXAMPLE If the TOLERABLE EXPOSURE (in µg/d) for a substance is known for an adult, then this reaches the adult PATIENT by the PATIENT breathing 20 m^3 of air in a day. Therefore, each cubic metre of air can contain as a maximum 1/20th of the TOLERABLE EXPOSURE value. This gives a permitted concentration (in µg/m^3) for that substance.

NOTE In calculating the dose to the PATIENT, it is the volume of breathing gas that the PATIENT inhales that is of interest — not the volume of gas flowing through the MEDICAL DEVICE. For example, sleep apnoea equipment or neonatal ventilators commonly have high flows, but only a portion of that enters the PATIENT's lungs — most of the flow is bypassed to the atmosphere.

The dose-to-PATIENT calculations for limited exposure use MEDICAL DEVICES, such as nebulizers or emergency resuscitation equipment (typically used for 20 min), cannot make use of the above calculations. The dose-to-PATIENT should be calculated on the actual clinically relevant delivered volumes. Therefore, the allowable concentrations of contaminants (in µg/m^3) in the breathing gas from short duration of use MEDICAL DEVICES can be higher than from continuous use MEDICAL DEVICES. Adjustments may be made for MEDICAL DEVICES not in continuous use (e.g. sleep apnoea therapy equipment). It is the total dose reaching the PATIENT in any 24 h period that is of importance.

Other breathing volume values, as appropriate for a specific MEDICAL DEVICE, may be used to calculate TOLERABLE EXPOSURE.

7 * Deriving allowable limits

7.1 General PROCESS

If compounds have been identified in the gas stream or condensate, then it shall be determined if the amount that can reach the PATIENT presents an acceptable RISK to that PATIENT.

Figure 3 illustrates the flowchart of PROCESS to derive inhalational TOLERABLE INTAKE (TI) for each identified compound.
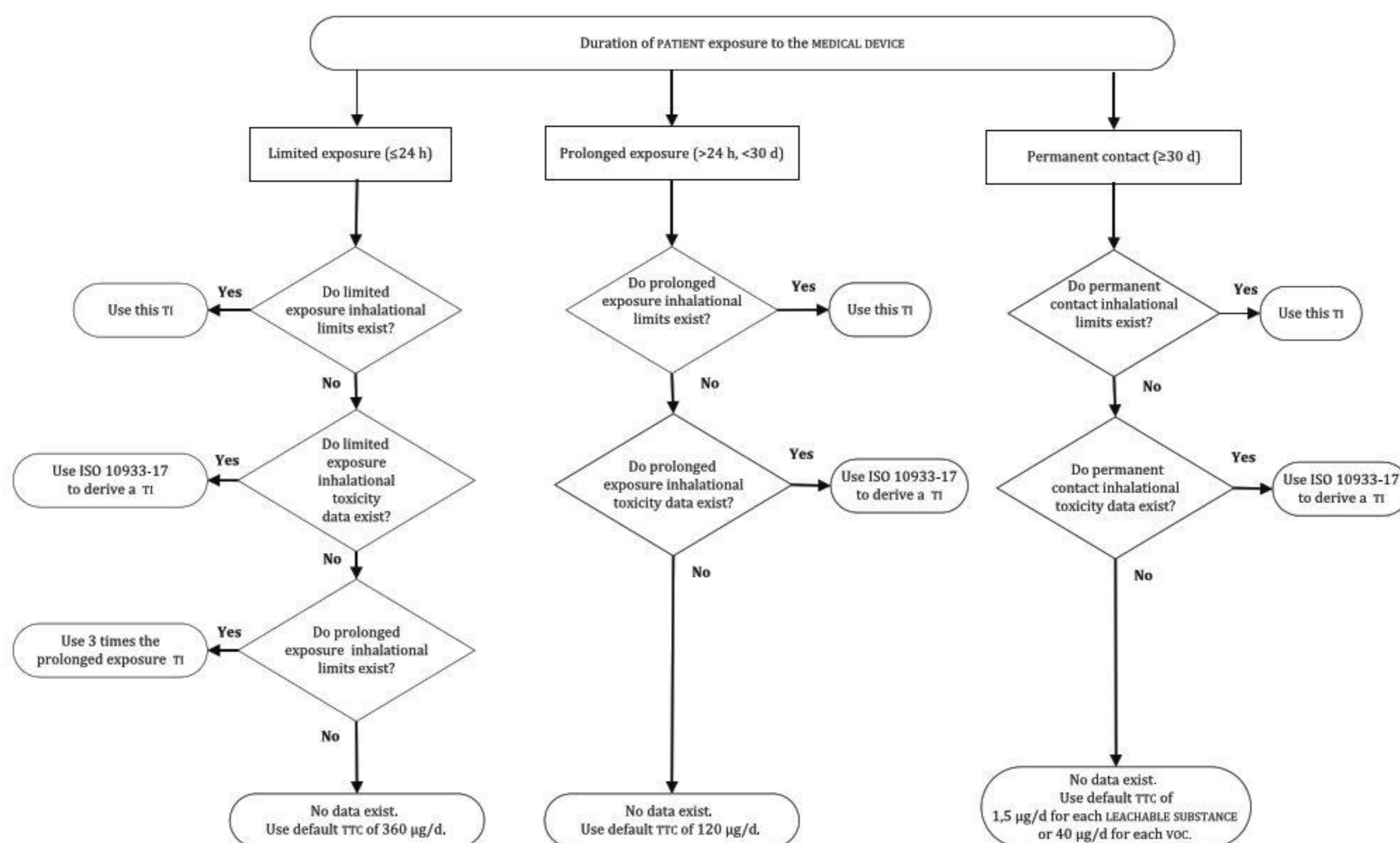
Figure 3 — Flowchart of PROCESS to derive inhalational TOLERABLE INTAKE (TI) for each identified compound

7.2 For MEDICAL DEVICES intended for limited exposure use (≤24 h)

For each identified compound:

— if possible, obtain limited exposure inhalational exposure limits for that compound from internationally accepted toxicological databases. Use this exposure limit in the assessment of BIOCOMPATIBILITY;

— if limited exposure inhalational exposure limits are not directly available, then seek data on limited exposure inhalational toxicity, and derive a TOLERABLE INTAKE (µg/kg body weight/d) for this compound using the procedure detailed in ISO 10993-17;

— if limited exposure inhalational toxicity data are not available, then seek prolonged exposure inhalational toxicity data, derive a TOLERABLE INTAKE (µg/kg body weight/d) for this compound using the procedure detailed in ISO 10993-17, and multiply this by 3 to adjust for the limited exposure duration;

— if no toxicity data are available, then a TTC (limited exposure) value of 360 µg/d can be used for an adult.

Use the PROCESS described in 6.2 (adjustment for body weight) to convert the TOLERABLE INTAKE (in µg/kg body weight/d) into a TOLERABLE EXPOSURE (in µg/d).

This PROCESS results in identifying an allowed dose-to-PATIENT, in µg/d, of this substance.

7.3 For MEDICAL DEVICES intended for prolonged exposure use (>24 h but <30 d)

For each identified compound:

— if possible, obtain prolonged exposure inhalational exposure limits for that compound from internationally accepted toxicological databases. Use this exposure limit in the assessment of BIOCOMPATIBILITY;

— if prolonged exposure inhalational exposure limits are not directly available, then seek data on permanent contact inhalational toxicity or carcinogenicity, and derive a TOLERABLE INTAKE (µg/kg body weight/d) for this compound;

— if no toxicity data are available, then a TTC (prolonged exposure) value of 120 µg/d may be used for an adult.

NOTE For the first 24 h period, the TTC is 360 µg; for subsequent 24 h periods, the TTC is 120 µg.

Use the PROCESS described in 6.2 (adjustment for body weight) to convert the TOLERABLE INTAKE (in µg/kg body weight/d) into a TOLERABLE EXPOSURE (in µg/d). This PROCESS results in identifying an allowed dose-to-PATIENT, in µg/d, of this substance.

7.4 For MEDICAL DEVICES intended for permanent contact (≥30 d)

For each identified compound:

— if possible, obtain permanent contact inhalational exposure limits for that compound from internationally accepted toxicological databases. Use this exposure limit in the assessment of BIOCOMPATIBILITY;

— if permanent contact inhalational exposure limits are not directly available, then seek data on permanent contact inhalational toxicity or carcinogenicity, and derive a TOLERABLE INTAKE (µg/kg body weight/d) for this compound;

— for VOCS, if no toxicity data are available, then a TTC (permanent contact) value of 40 µg/d may be used;

NOTE 1 For the first 24 h period, the TTC is 360 µg; for the subsequent twenty-nine 24 h periods, the TTC is 120 µg and thereafter 40 µg/d.

NOTE 2 A TTC of 40 µg/d represents the current state-of-the-art measurement threshold for VOCS. It represents an increase in the excess cancer RISK of 1 in $2,7 \times 10^{-4}$ as compared to 1 in $\times 10^{-5}$ for shorter exposures.

— for LEACHABLE SUBSTANCES, if no toxicity data are available, then a TTC (permanent contact) value of 1,5 µg/d may be used for an adult.

NOTE 3 For the first 24 h period, the TTC is 360 µg; for the subsequent twenty-nine 24 h periods, the TTC is 120 µg and thereafter 1,5 µg/d.

Use the PROCESS described in 6.2 (adjustment for body weight) to convert the TOLERABLE INTAKE (in µg/kg body weight/d) into a TOLERABLE EXPOSURE (in µg/d). This PROCESS results in identifying an allowed dose-to-PATIENT, in µg/d, of this substance.

8 RISK benefit analysis

If substances are identified, and their quantities are in excess of the basic TOLERABLE EXPOSURE LEVELS derived above, then the MANUFACTURER should review the materials and manufacturing PROCESSES. If that review cannot identify practicable alternative materials or PROCESSES, then the MEDICAL DEVICE may still be considered suitable if the benefits arising from the use of the MEDICAL DEVICE outweigh the RISKS posed to the PATIENT from this substance being present. RISK benefit analysis is particularly

applicable to critical life-saving MEDICAL DEVICES without which the PATIENT will die or for MEDICAL DEVICES for which there are no alternatives.

EXAMPLE The RESIDUAL RISKS of the MEDICAL DEVICE are similar to the RESIDUAL RISKS of other similar MEDICAL DEVICES that are legally marketable.

NOTE 1 ISO 14971:2007, 6.5 describes RISK/benefit analysis.

When the MANUFACTURER determines that the benefit outweigh the RISKS, the MANUFACTURER shall disclose the RESIDUAL RISK in the ACCOMPANYING DOCUMENT.

The MANUFACTURER shall document the results of RISK benefit analysis.

NOTE 2 Some AUTHORITIES HAVING JURISDICTION evaluate this RISK benefit analysis.

Check compliance by inspection of the RISK MANAGEMENT plan and RISK MANAGEMENT FILE.

9 Assess the BIOCOMPATIBILITY of the MEDICAL DEVICE

A BIOCOMPATIBILITY evaluation of a MEDICAL DEVICE is part of an overall RISK MANAGEMENT PROCESS.

The potential HAZARDS associated with the MEDICAL DEVICE shall be identified, and, in particular for the purposes of this document, the BIOCOMPATIBILITY HAZARDS arising from the GAS PATHWAYS shall be identified. The RISKS associated with those HAZARDS shall be assessed and a BIOCOMPATIBILITY evaluation plan developed.

Information relating to the substances released by the materials of the MEDICAL DEVICE shall be obtained. Possibly, tests are required to gather a full set of information. Refer to the subsequent parts of this document for particular tests and the analysis of results.

The dose that the PATIENT would receive in each day of use of the MEDICAL DEVICE shall be calculated for each substance of interest.

The TOLERABLE EXPOSURE for each of these substances shall be derived, following the procedure in Clause 7 of this document.

If the dose the PATIENT receives each day of each compound is less than the TOLERABLE EXPOSURE for that compound, then the MEDICAL DEVICE complies with this document.

If the dose to the PATIENT of one or more compounds exceeds the TOLERABLE EXPOSURE, but it is not practicable to alter the materials or manufacture, and the MANUFACTURER determines that the benefit outweigh the RISKS, then the MEDICAL DEVICE complies with this document.

NOTE Some AUTHORITIES HAVING JURISDICTION assess the BIOCOMPATIBILITY evaluation.

Annex A
(informative)

Rationale and guidance

A.1 General guidance

This annex provides rationale for the important requirements of this document and is intended for those who are familiar with the subject of this document but who have not participated in its development. An understanding of the reasons for the main requirements is considered to be essential for its proper application. Furthermore, as clinical practice and technology change, it is believed that rationale for the present requirements will facilitate any revision of this document necessitated by those developments.

The clauses and subclauses in this annex have been so numbered to correspond to the clauses and subclauses in this document to which they refer. The numbering is, therefore, not consecutive.

A.2 Rationale for particular clauses and subclauses

Subclause 5.1 — Duration of use

This document classifies exposure according to three durations of use:

— limited exposure: ≤24 h;

— prolonged exposure: >24 h and <30 d;

— permanent exposure: ≥30 d.

These times have been chosen to be consistent with the ISO 10993 series categories A, B and C for duration of use.

Subclause 6.3 — Deriving a permitted concentration from a TOLERABLE EXPOSURE

Data for minute ventilation in infants and children are found in Reference [9]. It has reference data for respiratory parameters in children, which were referenced from two publications, References [12] and [13]. These data are summarized in Table A.1.

The default body weight values used in this document are 0,5 kg for neonate, 3,5 kg for infant, 10 kg for paediatric and 70 kg for adult PATIENT. The default breathing volumes are 0,21 m^3/d, 2 m^3/d, 5 m^3/d, and 20 m^3/d, respectively.

Table A.1 — Ventilation data by body size

PATIENT size	Body weight (BW) kg	Proposed total ventilation for VOC dose m^3/d
Neonate	0,21	0,5
Infant	3,5	2,0
Paediatric	10	5,0
Adult (≥19 years old)	70	20

Clause 7 — Deriving allowable limits

The choice of a TTC level (adult with 70 kg body weight) for unknown substances of 360 µg/d (limited exposure), 120 µg/d (prolonged exposure) and 1,5 µg/d (permanent contact) was discussed at length by the committee. For lower body weight PATIENTS, a PATIENT-specific TTC value (µg/d) based on the PATIENT body weight from Table A.1 should be derived.

The inhalation TTC value for prolonged (24 h to 30 d) exposure to VOCS released into the GAS PATHWAY is based on:

— the 5th percentile of a distribution of noncancer TOLERABLE INTAKE (TI) values derived from inhalation NOAEL (no observed adverse effect level) and LOAEL (lowest observed adverse effect level) values (exposure duration ≤30 d) reported in the RepDose database (135 µg/d)[14];

— the acceptable intake of an individual mutagenic impurity in a pharmaceutical product with exposure to the PATIENT for ≤30 d, per the IC H M7 guidance[15] (120 µg/d).

The lower of the two values, 120 µg/d, was selected as the inhalation TTC value for prolonged exposure and this value is intended to be protective for both cancer and noncancer effects.

Recognizing that exposure limits can be adjusted to permit higher levels of exposure for shorter durations, the prolonged inhalation TTC was adjusted upwards to derive a limited exposure duration TTC of 360 µg/d using a modification of Haber's Rule ($C \times T^n = k$)[16]. Briefly, an exponent of $n = 0.33$ was used to estimate an airborne concentration (C) of a VOC that produces an equivalent toxicological response in 24 h to that seen after inhalation exposure to 120 µg/d for 30 d. The three-fold increase in the limited exposure duration TTC compared to the TTC for prolonged exposure is consistent with similar efforts to extrapolate exposure limits from longer to shorter durations.

Lastly, the committee considered permanent exposure limits for adults (70 kg) and proposed 40 µg/d.

Taking a practical approach, the committee discussed the levels at which it was currently possible to measure concentrations using established, standardized laboratory techniques. The current detection limit for VOCs using standardized test methods is 2 µg/m^3. Thus, a proposed limit of 2 µg/m^3 as a concentration is as low as possible to measure. A concentration of 2 µg/m^3 gives a total dose-to-PATIENT for an adult (who breathes 20 m^3/d) of 40 µg. Thus, if any TTC limit below 40 µg/d were to be proposed, it would be meaningless, as it would not be possible to measure it.

It is recognized that these limits can be adjusted in the future as more knowledge becomes known and analytical measurement techniques improve. However, on the balance of probabilities, the committee felt that the proposed limits of 360 µg/d (limited exposure duration), 120 µg/d (prolonged exposure duration) and 40 µg/d (permanent exposure duration) were reasonably conservative and would not expose PATIENTS to unacceptable RISKS.

These limits apply only to substances added by the MEDICAL DEVICE to gases supplied to PATIENTS. The proposed limits are not relevant to any other type of PATIENT exposure.

Annex B
(informative)

Reference to the essential principles

This document has been prepared to support the essential principles of safety and performance of GAS PATHWAYS as components of MEDICAL DEVICES according to ISO 16142-1[6]. This document is intended to be acceptable for conformity assessment purposes.

Compliance with this document provides one means of demonstrating conformance with the specific essential principles of ISO 16142-1[6]. Other means are possible. Table B.1 maps the clauses and subclauses of this document with the essential principles of ISO 16142-1.

Table B.1 — Correspondence between this document and the essential principles

Essential principles of ISO 16142-1[6]	Corresponding clause(s)/ subclause(s) of this document	Qualifying remarks/notes
8.1 a)	Clause 4, Clause 5, Clause 6, Clause 7, Clause 8, Clause 9	Only the part relating to toxicity is addressed.
8.1 b)	Clause 4, Clause 5, Clause 6, Clause 7, Clause 8, Clause 9	
8.2	Clause 4, Clause 5, Clause 6, Clause 7, Clause 8, Clause 9	
8.4	Clause 4, Clause 5, Clause 6, Clause 7, Clause 8, Clause 9	
8.5	Clause 4, Clause 5, Clause 6, Clause 7, Clause 8, Clause 9	Only the part relating to egress of substances from the MEDICAL DEVICE is addressed.

Annex C
(informative)

Terminology — Alphabetized index of defined terms

NOTE The ISO Online Browsing Platform (OBP) and the IEC Electropedia provide access to many of these terms and definitions.

Term	Source
ACCESSORY	3.1
ACCOMPANYING DOCUMENT	ISO 14971:2007, 2.1
AUTHORITY HAVING JURISDICTION	ISO 16142-1:2016, 3.1
BIOCOMPATIBILITY	3.2
EXPECTED SERVICE LIFE	3.3
FORMULATION	3.4
GAS PATHWAY	3.5
HAZARD	ISO 14971:2007, 2.3
INTENDED USE	ISO 14971:2007, 2.5
LEACHABLE SUBSTANCE	3.6
MANUFACTURER	ISO 14971:2007, 2.8
MEDICAL DEVICE	3.7
MEDICAL GAS PIPELINE SYSTEM	ISO 7396-1:2016, 3.36
NORMAL CONDITION	3.8
NORMAL USE	3.9
PARTICULATE MATTER	3.10
PARTICULATES	3.10
PATIENT	3.11
PM	3.10
PROCESS	ISO 14971:2007, 2.13
RESIDUAL RISK	ISO 14971:2007, 2.15
RISK	ISO 14971:2007, 2.16
RISK ANALYSIS	ISO 14971:2007, 2.17
RISK ASSESSMENT	ISO 14971:2007, 2.18
RISK MANAGEMENT	ISO 14971:2007, 2.22
RISK MANAGEMENT FILE	ISO 14971:2007, 2.23
TE	3.13
THRESHOLD OF TOXICOLOGICAL CONCERN	3.12
TI	3.14
TIL	3.14
TOLERABLE EXPOSURE	3.13
TOLERABLE INTAKE	3.14
TOLERABLE INTAKE LEVEL	3.14
TTC	3.12
TYPE TEST	3.15
VOC	3.16

Term	Source
VOLATILE ORGANIC COMPOUND	3.16
VERY VOLATILE ORGANIC COMPOUND	3.17
VVOC	3.17

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[2] ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices*

[3] ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics*

[4] ISO 10993-15, *Biological evaluation of medical devices — Part 15: Identification and quantification of degradation products from metals and alloys*

[5] ISO 13485:2016, *Medical devices — Quality management systems — Requirements for regulatory purposes*

[6] ISO 16142-1:2016, *Medical devices — Recognized essential principles of safety and performance of medical devices — Part 1: General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the selection of standards*

[7] ISO/IEC 17025, *General requirements for the competence of testing and calibration laboratories*

[8] IEC 60601-1:2005+AMD1:2012, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*

[9] BS 5724-3.12, *Medical electrical equipment — Particular requirements for performance — Method of declaring parameters for lung ventilators*

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